REMARKS

Reconsideration of the allowability of the present application is requested respectfully.

Status of the Claims

Claims 21 to 25, 27 to 31, 33, 35, 38, and 39 were acted upon by the Examiner in the Office Action dated January 30, 2003. No claims are withdrawn. Claims 21, 24, 28, 30, and 35 have been amended. No claims have been canceled. Claims 41 and 42 have been added. Accordingly, Claims 21 to 25, 27 to 31, 33, 35, 38, 39, 41, and 42 are presented for examination.

The amendments to Claims 21, 24, 28, and 30 are editorial in nature and as such do not constitute the addition of new matter. Claim 35 has been amended to depend from Claim 33 instead of canceled Claim 34.

Support for newly added Claims 41 and 42 may be found throughout the application, particularly on page 14, line 4, to page 17, line 5.

ARGUMENTS

In response to the Examiner's Office Action dated January 30, 2003, Applicant respectfully traverses the Examiner's rejection of Claims 21 to 25, 27 to 31, 33, 35, 38, and 39.

The §103(a) Rejections

The Rejection of Claims 21 to 25, and 27

The Examiner has rejected Claims 21 to 25, and 27 under 35 U.S.C. §103(a) as being unpatentable over Jones et al. (Infect. Immun., 1996, 64(2): 489-494) in view of Shahin et al. (Infect. Immun., 1995, 63(4):1195-1200).

Applicant respectfully traverses the rejection.

MPEP §2143 states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In the present case there is no reasonable expectation that a combination of Jones et al. and Shahin et al. would be successful. Furthermore, as required by MPEP §2143, the teaching to make the claimed combination as well as the expectation of success is not found in either Jones et al. or Shahin et al.

Claim 21 covers a method of inducing a protective immune response, requiring oral administration of a first and a second subpopulation of microparticles, wherein each of said microparticles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable polymer, and wherein the antigen in the microparticles of the first subpopulation is different than

the antigen in the microparticles of the second subpopulation and at least 50% of the microparticles are less than 5 μm. Claims 22 to 25 and 27 all depend from Claim 21.

Jones et al. is directed to oral administration of microencapsulated *B. pertussis* fimbriae. Jones et al. teaches that administration of *B. pertussis* vaccines to the respiratory tract is not effective in stimulating production of serum immunoglobulins. Furthermore, Jones et al. speculates that in regard to administration to the respiratory tract, "an unequivocal correlation between the presence of secretory antibodies and protection has not been established" (Jones et al., page 491, col. 2, para. 2, lines 13 to 14). Jones et al. also states that intranasal administration of *B. pertussis* vaccines "may not be appropriate for inducing immunity" (Jones et al., page 491, col. 2, para. 2, line 25).

In contrast, Shahin et al. discloses intranasal administration of the secreted *B. pertussis* proteins FHA, pertussis toxin, and pertactin. Shahin et al. states that administration of microencapsulated FHA fails to stimulate "a protective mucosal response via the oral route" (Shahin et al., page 1199, col. 2, para. 2, lines 12 to 13). Shahin et al. also discloses that "less than 1% of an oral dose of DL-PLG microspheres successfully reaches the Peyer's patch", indicating that oral administration of microspheres is a poor route for inducing immunity (Shahin et al., page 1199, col. 2, para. 2, lines 15 to 16). Furthermore, Shahin et al. states that "Respiratory immunization with antigens...has been a successful strategy for the induction of both systemic and mucosal immune responses" (Shahin et al., page 1199, col. 2, para. 3, lines 1 to 3).

Accordingly, a careful reading of Jones et al. and Shahin et al. reveals that although these publications were published within ten months of each other, they directly contradict each other. Jones et al. teaches oral administration of vaccines since respiratory administration does not work, while Shahin et al. teaches respiratory (intranasal) administration of vaccines because oral administration does not work.

MPEP §2141 states (emphasis added), "The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination". In

considering Jones et al. and Shahin et al. in their entireties, it is clear that these two publications are not only in direct conflict with each other, they teach away from each other. The Examiner states that one of skill in the art would have chosen to use the oral route taught by Jones et al. as opposed to an intranasal route, because Jones et al. discloses that the oral route is better. However, the Examiner provides no basis why one of skill in the art would discount the teachings of Shahin et al., which teaches exactly the opposite, that the intranasal route is superior, particularly when using FHA as antigen. Applicant respectfully submits that the present obviousness rejection is based on a hindsight reconstruction of the present invention. As noted above, the publications must be considered as a whole. The Examiner has presented no objective evidence that, without the present application to use a guide, one of skill in the art would, upon reviewing Jones et al. and Shahin et al., have selectively ignored those portions of Jones et al. and Shahin et al. that are in conflict with each other. Without the present application in front of them, one of skill in the art would have no basis to follow Jones et al. and discount Shahin et al. Applicant submits that one of skill in the art would 1) not combine publications that teach away from each other; and 2) not be expected to be successful should they make such a combination.

Applicant also submits that one of skill in the art, when critically reading the data in Shahin et al., would not have an expectation of success based upon the presented data. In particular, the data allegedly supporting the claim in the abstract of Shahin et al. (administration of more than one antigen is more effective administering only one antigen) is insufficient to support an expectation of success. Table 7 on page 1199 of Shahin et al. discloses the Log_{10} CFU from the lungs and trachea of mice treated intranasally with different combinations of antigens. Taking standard deviations into account, only two combinations (FHA, PT, + pertactin and FHA + pertactin) have results that are better than administration of single antigens. However, in the FHA, PT, + pertactin combination, the results for only 2 out of 7 (lungs) and 1 out of 7 (trachea) infected mice are shown. Similarly, in the FHA + pertactin mice, the results for only 2 out of 5 and 1 out of 5 for lungs and trachea, respectively, are shown. The authors provide no explanation for their selective omission of the data for the other infected mice. Applicant respectfully submits that one of skill in the art would question to why the data from the other mice was omitted and accordingly would be skeptical as to the veracity of the data and the conclusions drawn therefrom. Thus, applicant respectfully submits that one of skill in the art would not

consider Shahin et al. as a valid teaching of more than one antigen being more effective than administering only one antigen and based upon this data would not have an expectation of success.

MPEP §2141 further states (emphasis added):

> Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence.

In contrast to the Shahin et al. data, Figure 6 of the present application demonstrates, using all of their mice (see Example 7 on pages 20 to 21), that after 14 days, PT +FHA gives better than 2 Log_{10} units improvement over PT alone. Thus, in comparison to the results of Shahin et al., this result demonstrates unexpected results (applicant's data, surprisingly, shows synergism), the satisfaction of a long felt need (improved vaccination), and failure of others (the data supporting the claims of Shahin et al. are very weak).

In view of the lack of a motivation to combine Jones et al. and Shahin et al.; the lack of any expectation of success should such a combination be made; and the secondary considerations of long felt need, failure of others, and unexpected results applicant respectfully requests the withdrawal of the rejection of Claims 21 to 25, and 27 under 35 U.S.C. §103(a).

The Rejection of Claims 28 to 31, 33, and 35

The Examiner has rejected Claims 28 to 31, 33, and 35 under 35 U.S.C. §103(a) as being unpatentable over Jones et al. in view of Shahin et al., and in further view of Singh et al. (Vaccine, 1998, 16(4): 346-352) or O'Hagan et al. (US 5,603,960).

Applicant respectfully traverses the rejection.

Claim 28 covers a method of inducing a protective immune response, requiring oral administration of a first and a second subpopulation of microparticles, wherein each of said microparticles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable

polymer, and wherein the antigen in the microparticles of the first subpopulation is different than the antigen in the microparticles of the second subpopulation and at least 50% of the microparticles are less than 600 nm. Claims 29 to 31, 33, and 35 all depend from Claim 28.

The incompatibility of the teachings of Jones et al. with Shahin et al. is discussed above. Singh et al. and O'Hagan et al. have been applied for the teaching of a nanospheres with mean sizes of "about 500nm" and "between 200 nm and 200 μm", respectively. These teachings provide no basis to overcome the deficiencies of Jones et al. and Shahin et al. Since Singh et al. and O'Hagan et al. do not provide any information that overcomes the deficiencies in the other cited publications, applicants request respectfully withdrawal of the obviousness rejection of Claims 28 to 31, 33, and 35 which besides Jones et al. and Shahin et al., additionally relies on Singh et al. and O'Hagan et al.

Furthermore, the Examiner has implied that Singh et al. not only discloses two antigens encapsulated in a single microparticle, but also that Singh et al. discloses two or more batches of microparticles with "different rates of antigen" (page 6 of the present action). Applicant submits that if the Examiner is implying that Singh et al. discloses two subpopulations of microparticles containing different antigens, then the Examiner is incorrect. Singh et al. discloses that "two or more batches of microparticles with different rates of antigen release may be prepared and combined to provide a single dose vaccine" (Singh et al., page 347, col., 1, para. 1, lines 11 to 14, emphasis added). The present action omits the word "release" when quoting this passage. This passage refers to a single antigen being released at different rates by differently sized microparticles. Singh et al. does not teach that having different antigens in different microparticles is beneficial. Indeed, Singh et al. teaches that "the presence of more than one antigen in a multi-component vaccine may result in reduced immunogenicity for all the antigens" (Singh et al., page 350, col., 2, para. 3, lines 7 to 10, emphasis added). Thus, a review of the entire publication, as required by MPEP §2141, indicates that Singh et al. teaches away from using more than one antigen, under any circumstances. Thus, one of skill in the art would not combine Singh et al. with Shahin et al. since Shahin et al. asserts (albeit an unsupported assertion) that more than one antigen improves immunogenicity.

Singh et al. and O'Hagan et al. do not overcome the deficiencies of Jones et al. and Shahin et al., as noted above. Furthermore, since they teach away from each other, one of skill in the art would not be motivated to combine to combine Singh et al. and Shahin et al. In view of these arguments, applicant respectfully requests the withdrawal of the rejection of Claims 28 to 31, 33, and 35 under 35 U.S.C. §103(a).

The Rejection of Claim 38

The Examiner has rejected Claim 38 under 35 U.S.C. §103(a) as being unpatentable over Jones et al. in view of Shahin et al., and in further view of Andrianov (US 5,807,757).

Applicant respectfully traverses the rejection.

Claim 38 covers the method of Claim 21 wherein the microparticles in each subpopulation are formed by coacervation.

The incompatibility of the teachings of Jones et al. with Shahin et al. is discussed above. Andrianov has been applied for the teaching of a method for preparing polyphosphazene microspheres by coacervation. This teaching provides no basis to overcome the deficiencies of Jones et al. and Shahin et al. Since Andrianov does not provide any information that overcomes the deficiencies in the other cited publications, applicants request respectfully withdrawal of the obviousness rejection of Claims 38 which besides Jones et al. and Shahin et al., additionally relies on Andrianov.

The Rejection of Claim 39

The Examiner has rejected Claim 39 under 35 U.S.C. §103(a) as being unpatentable over Jones et al. in view of Shahin et al., in view of Singh et al. or O'Hagan et al., and in further view of Andrianov.

Applicant respectfully traverses the rejection.

Claim 39 covers the method of Claim 28 wherein the nanoparticles in each subpopulation are formed by coacervation.

The incompatibility of the teachings of Jones et al. with Shahin et al., the deficiencies of Singh et al. and O'Hagan et al., and the incompatibility of Singh et al. and Shahin et al. are discussed above. Andrianov has been applied for the teaching of a method for preparing polyphosphazene microspheres by coacervation. This teaching provides no basis to overcome the deficiencies and incompatibilities of the other cited publications. Since Andrianov does not provide any information that overcomes the deficiencies in the other cited publications, applicants request respectfully withdrawal of the obviousness rejection of Claim 39 which besides Jones et al., Shahin et al., Singh et al. and O'Hagan et al., additionally relies on Andrianov.

Respectfully submitted,

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